P. ENT COOPERATION TREA.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 22 August 2000 (22.08.00)	
International application No. PCT/NL98/00722	**Applicant's or agent's file reference** BO 42134
International filing date (day/month/year) 21 December 1998 (21.12.98)	**Priority date** (day/month/year)
Applicant POELSTRA, Klaas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 July 2000 (18.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

Nederlandsch Octrooibureau
Anno 1888

Octrooigemachtigden
European Patent Attorneys

Merken- & Modellen-
gemachtigden
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Attorneys

EUROPEAN PATENT OFFICE
Directorate General 2
Erhardtstrasse 27
D-80298 MÜNCHEN 2
c/o P.O. Box 5818
2280 HV RIJSWIJK

Your ref.
Our ref. BO 42134 PCT AT/aw

The Hague, 19 January 2001

Re: International Patent Application No. PCT/NL98/00722;
Applicant: Stichting voor de Technische Wetenschappen et al.

Dear Sir,

Further to the Written Opinion issued in the above mentioned case please be advised we are grateful to note the Examiners acceptance of claims 2-23 as being patentable.

The Examiner has raised some objections to the remaining claims and we shall provide our comments in the same order as the objections in the Written Opinion.

Objection III.1

Claim 25' has been amended such that the meaning thereof is now clear. The term ligand is no longer present. Claim 25' has been renumbered to claim 26. The words "with the proviso the ligand is" have been replaced by the words "as active compound with the proviso the active compound is" (A basis for this amendment is i.a. present in claims 28 and 29 as filed).

Claim 26 as filed has been renumbered to claim 27.

Claim 27 has been amended and renumbered as claim 28. The claim has been split into two claims. The second claim being new claim 29. The basis for these amendments can be found on page 7 lines 25-27 of the description as filed and page 3 lines 15-21. The

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amendment to Claim 27 as filed reads as new claim 28 and new claim 29:

28. A method of purification of AP itself from tissue or bodily fluids or other biological system with a ligand which binds to the LPS binding site of AP.

29. A method according to claim 28 wherein the ligand is LPS, lipid A or ligand described in the preceding claims.

The amendment to claim 27 as filed also overcomes the objections to old claims 28 and 29 as filed. Claims 28 and 29 as filed have been renumbered 30 and 31 respectively and are formulated as second medical use claims.

Objection III.2

The objection concerning method of treatment being excluded for Europe under EPC is noted for claim 25' as filed. As however USA PTO e.g. does allow such claims the claim is currently maintained. We also enclose second medical use claims covering the subject matter of claim 25' as filed in the form of new claims 30 and 31.

The objection to claims 26 and 27 as filed has also been noted and new claims 32-36 have been added wherein the restriction to in vivo situations has been introduced as suggested by the Examiner. The basis for the various samples can be found on page 5, lines 25-26, page 6 lines 15-22 and page 7 lines 20-27. See also for new claim 32 the discussion concerning claim 26 as filed, in particular with regard to new claim 25 as this is a corresponding claim with in vitro restriction.

The objection to claims 28 and 29 as filed has been overcome by reformulating them to second medical use claims. These claims have been renumbered as claims 30 and 31.

Objection V.1.1

Claim 24 as filed has been amended by removal of the optional character of the elements. Claim 25 has been deleted and a new method claim inserted. We argue that the inclusion of the element "instructions" in a kit in combination with a compound is ad-

missible under EPO regulations. The presence of the element "instructions" in the claim is essential for the technical effect. The technical effect of the invention is achieved by the compound per se in it's specific application and interpretation for use in a method according to the other claims. The technical effect is a previously unrecognised effect of the known compound. The data carrier provides the elements required to use the known compound in the manner corresponding to the novel claimed methods. There clearly is a claim provided with an element providing a technical effect i.e. the data carrier.

We also point to recent case law in the software field regarding patentability of data carriers and refer to cases T97/0935 and T97/1173 and suggest analogous reasoning could be applied here also.

Furthermore we point out that such claims appear to be patentable e.g. in USA and thus for this reason also the claim is maintained.

Objection V.1.2

Claim 40 is silent with regard to any mechanism via which the compounds of the invention of D1 work to arrive at reduction of toxic effects of endotoxin. Claim 40 thus is silent on the process of LPS removal. Claim 26 as filed (now amended claim 27) is however specifically directed at the process of LPS removal. This element is explicitly described in the claim. Admittedly inadvertently it is the case that the compounds of D1 will bind to LPS in the process disclosed in D1 BUT D1 does not disclose the step of separating the substance with toxic activity and the compound with phosphatase activity. Thus neither claim 40 nor D1 literally disclose the subject matter of claim 26 as filed.

At the worst claim 40 could be considered an inadvertent disclosure of a genus with a breadth of claim overlapping the process of claim 26. However the disclosure of a genus is not novelty destroying for a purposive selection of a species or range of species falling within the genus. So the additional requirement of the separation step which is

purposive for removing LPS as defined in claim 26 as filed clearly provides novelty over claim 40.

In addition to the above the disclaimer of claim 26 as filed also provides a further distinction over the disclosure of D1. Claim 40 of D1 covers a process wherein the compound that is applied has phosphatase activity. Phosphatase activity of D1 is synonomous with dephosphorylating activity. Claim 26 as filed explicitly disclaims the use of compounds with dephosphorylating activity. Thus claim 26 describes a process using different compounds to those used in the process according to D1.

A further new claim 25 has been introduced which is identical to claim 26 as filed with the exception the disclaimer is absent. As stated above the novelty of such a process is present over D1. The basis for such amendment can be found in the description page 3 line 15-18, lines 22-33 and also page 7 lines 21-23 and page 8 lines 10-12.

Objection Item VII

We point to rule 34 (1) c as discussed in the Guidelines in Part C, chapter II page 4. This states since the reader is presumed to have the general background technical knowledge appropriate to the art, the examiner should not require the applicant to insert anything in the nature of a treatise or research report or explanatory matter which is obtainable from textbooks or is otherwise well known. Likewise the examiner should not require a detailed description of the content of cited prior art documents. The person skilled in the art has thousands of publications available describing how to determine alkaline phosphatase activity. The two prior art documents cited are merely provided as a courtesy to give two examples of potential sources of the required information. The reference that their contents are incorporated by reference in the context of page 5 line 23 is perfectly sufficient for the skilled person to retrieve the required data.

Furthermore Example III provides a further illustration of a suitable method. Thus the requirement of enablement is clearly fulfilled without the skilled person needing to

carry out undue search for a method to ascertain AP activity. The skilled person can readily get aquainted with this technique.

Objection Item VIII.1

The claims have been renumbered taking this objection into account.

Objection Item VIII.2

Claim 1 has been amended as suggested for AP and LPS abbreviations.

Objection Item VIII.3

We point to page 6 of the description where an alternative to the method of claim 2 is presented. We also point to the fact that the method can also be used to follow the course of disease by taking a first sample, treating the patient with LPS binding compound and taking a second measurement and assessing whether the level has decreased. In this instance one need not compare the sample to that of a healthy individual one merely needs to assess decrease in value as being indicative of the disease being present and subsequently responding to the treatment. If the disease were absent when the first sample was taken then the second sample would show a same value after treatment with LPS in between the sample times. Thus it is submitted that restriction to claim 2 would deny a scope of protection to which patentee is entitled and thus claim 1 is maintained. We refer in this instance to the description on page 6 lines 23-30.

Objection VIII.4

Example III provides the required support as does Example IV. Dephosphorylated LPS binds to the active site of alkaline phosphatase because MPLA (monophosphoryl Lipid A) attenuates the enzyme activity.

Our ref. BO 42134 PCT AT/aw 19 January 2001

Reconsideration of the objections raised in the Written Opinion is hereby requested in the light of the amended claims and elucidation provided herein.

The representative,

Anne J. Taylor

Encl.: amended claims 1-36 (3-f.)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/NL 98/00722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/569 G01N33/573 G01N33/567 G01N33/579 C12N9/16
A61K31/715 C12Q1/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C12N A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 05455 A (RIJKSUNIVERSITEIT TE GRONINGEN) 23 February 1995 (1995-02-23) page 2, line 3 - line 14 page 3, line 29 - line 36	1-24
Y	page 15, line 5 - line 30	25-29
Y	CHEMICAL ABSTRACTS, vol. 126, no. 23, 9 June 1997 (1997-06-09) Columbus, Ohio, US; abstract no. 302513, XP002113176 last line of abstract & K. POELSTRA ET AL.: "A physiological function for alkaline phosphatase: endotoxine detoxification" LABORATORY INVESTIGATION, vol. 76, no. 3, 1997, pages 319-327, St. Louis MI USA	25-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1999	07/09/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Van Bohemen, C

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No
PCT/NL 98/00722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505455 A	23-02-1995	AU 1424399 A	01-04-1999
		AU 4835693 A	14-03-1995
		AU 698331 B	29-10-1998
		AU 7710194 A	14-03-1995
		EP 0721501 A	17-07-1996
		WO 9505456 A	23-02-1995

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
BO 42134		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/NL 98/00722	21/12/1998	
Applicant		
STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN; et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   DIAGNOSIS OF SEPSIS USING THE LPS-BINDING MOIETY OF ALKALINE PHOSPHATASE

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

PATENT COOPERATION TREATY

PCT

From the Gemäß Bewerken
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JORRITSMA, Ruurd et al.
NEDERLANDSCH OCTROOIBUREAU
Scheveningseweg 82
(P.O. Box 29720)
NL-2502 LS The Hague
PAYS-BAS

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	07.08.00
Applicant's or agent's file reference: BO 42134	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL 98/00722	21/12/1998	21/12/1998

Applicant: STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN et al.

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

18/07/2000

2. This date of receipt is:

☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

☐ *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	CHAVONAND F H Tel. (+49-89) 2399-2390

EUROPÄISCHES PATENTAMT · EUROPEAN PATENT OFFICE · OFFICE EUROPÉEN DES BREVETS

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To: Mr. L.C. de Bruijn
NEDERLANDSCH OCTROOIBUREAU
Scheveningseweg 82
2517 KZ Den Haag

PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing *(day/month/year)*
08 January 1999 (08.01.99)

Applicant's or agent's file reference
BO 42134

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL98/00722	21 December 1998 (21.12.98)	

Applicant
Stichting voor de Technische Wetenschappen et al

Title of the invention
The LPS-binding moiety of alkaline phosphatase as a diagnostic tool in patients with sepsis

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

[X] was transmitted to the International Bureau on 13 January 1999 (13.01.99)

[ ] has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau *:

[ ] because the necessary national security clearance has not yet been obtained.

[ ] because *(reason to be specified)*:

* The international Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c))

Name and mailing address of the receiving Office	Authorized officer
Bureau voor de Industriële Eigendom P.O. Box 5820 2280 HV Rijswijk The Netherlands	R. Blokdijk
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PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

JORRITSMA, Ruurd et al.
NEDERLANDSCH OCTROOIBUREAU
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(P.O. Box 29720)
NL-2502 LS The Hague
PAYS-BAS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

by Airmail Post

Date of mailing *(day/month/year)*	30.04.2001
Applicant's or agent's file reference BO 42134	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL98/00722	21/12/1998	21/12/1998

Applicant
STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

corrected version

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Authorized officer
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BO 42134		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NL98/00722	21/12/1998	21/12/1998
International Patent Classification (IPC) or national classification and IPC G01N33/569		
Applicant STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/07/2000	30.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Tilkorn, A-C Telephone No. +49 89 2399 8688

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL98/00722

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-12	as originally filed				

Claims, No.:

1-36	as received on	19/01/2001	with letter of	19/01/2001	

Drawings, sheets:

1/1	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 25-27,30,31,33 with regard to novelty, inventive step and industrial applicability and 28,29,36 with regard to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 25-29,36 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 30,31 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☒ the claims, or said claims Nos. 26,27,33 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23,28,29,32,34-36
	No:	Claims	24
Inventive step (IS)	Yes:	Claims	1-23,28,29,32,34-36
	No:	Claims	24
Industrial applicability (IA)	Yes:	Claims	1-24,32,34,35
	No:	Claims	-

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III:

1 **Claims 26-29** and **36** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT because they relate to methods which might be carried out in vivo. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2 **Claim 25** does not comply with Art 5 PCT, because there is no technical support for a compound having the LPS binding site of alkaline phosphatase excluding alkaline phosphatase (AP) or a derivative having dephosphorylating activity. Moreover, there is no guidance given in the application which would enable the skilled person to produce such a compound. Therefore no opinion is given as to novelty, inventive step and industrial applicability of claim 26. The same argument applies to **claims 26, 27** and **33**.

3 **Claims 30** and **31** are so unclear, that no meaningful opinion can be formed on novelty and inventive step (Art 34(4)(a)(ii) PCT; Guidelines VI-5.11). The claims are directed to the use of a compound that has the LPS binding site of alkaline phosphatase. Examples given are ligands of AP. However, the compound can either have the LPS binding site of AP or it can be a ligand of AP. In other words compounds with an LPS binding site of AP are the counterparts of LPS, lipid A and other AP ligands. Thus, **claims 30** and **31** are contradictory in themselves and their subject-matter is not defined.

Re Item V

The following documents are referred to in this communication:

D1: WO 95 05456 A (cited in the application: p 2 l 24; p 3 l 3)

1 Novelty (Art 33(2) PCT):

1.1 **Claim 24** is not novel for the following reasons:
A kit alone is not considered to contain a technical feature. Alkaline phosphatase

ligands are known in the art, e.g. lipid A (see e.g. D1: p 1 l 25-27; p 11 l 26-33) . Instructions for carrying out an assay are not considered to be a technical feature. Moreover, the alkaline phosphatase ligand has to be in a buffer and a container. Taken together, all the technical features of claim 24 are anticipated by the disclosure of D1.

1.2 **Claim 1** is novel, because none of the available documents discloses a method of diagnosis of sepsis or endotoxemia by monitoring the degree of occupancy of LPS binding sites on alkaline phosphatase in a sample. Accordingly, **claims 2-23** and **36** are novel.

1.3 **Claim 28** is novel, because the available prior art does not describe a method for purification of AP from tissue or fluid samples that uses a ligand which binds to the LPS binding site of AP. **Claims 29, 34** and **35** are novel accordingly.

1.4 **Claim 32** is novel, because the prior art does not describe a method for removing LPS from tissue or fluid samples that involves the separation of LPS bound to AP from the tissue or fluid sample.

2 Inventive Step (Art 33(3) PCT):

2.1 The subject-matter of **claim 1** seems to satisfy Art 33(3) PCT:
The present invention is based on the observation of product inhibition of alkaline phosphatase (p 10 experiment IV). The concept of the invention thus consists of determining the ratio of active alkaline phosphatase to non-active ligand bound AP (p 5 l 13-22) in order to diagnose gram negative bacterial infection.
D1, which is considered to represent the closest prior art, describes the correlation between alkaline phosphatase activity and gram negative bacterial infection namely the increase in AP activity due to gram negative bacterial infection.(D1: Fig. 6 p 21 l 32- p 22 l 7). AP activity is measured with standard methods.
The problem to be solved by the method of claim 1 can thus be regarded as the provision of an alternative method for the diagnosis of endotoxemia or sepsis due to gram negative bacterial infection.
Since the product inhibition of AP was not known at the priority date, the claimed method is not rendered obvious by any piece of prior art.

Accordingly, **claims 2-23** seem to be inventive, too.

2.2 **Claims 28** and **29** appear to be inventive (Art 33(3) PCT) because there is no indication found in the available state of the art that would render the purification of AP from tissue or body fluids with a ligand that binds to the LPS binding site of AP obvious. The same argument applies to **claims 34-36**.

2.3 **Claim 32** seems to meet the requirements of Art 33(3) PCT for the following reasons:
D1 (claim 40), which is considered to represent the closest prior art, is distinguished from the subject-matter of claim 32 in that the method disclosed in claim 40 of D1 does not include a separation step which removes the endotoxin bound to AP from the tissue or fluid sample.
The problem to be solved in claim 32 can thus be regarded as the provision of an alternative method for removing LPS from a tissue or fluid sample.
There is no indication found in the prior art, which would render a method that encompasses the separation of LPS bound AP from the sample obvious.

3 Industrial applicability (Art 33(4) PCT):

For the assessment of the present **claims 25-31** and **36** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

The expression "incorporated herein by reference" in respect of prior art documents (e.g. page 5 l 23, page 6 l 12) leads to a doubt as to whether the requirement of the description being self-contained is satisfied (Guidelines II, 4.17).

Re Item VIII

1 The additional technical feature contained in **claim 2** consists of the assessment of the result obtained by determining the degree of AP occupancy of LPS binding sites on alkaline phosphatase (claim 1) and thus appears to be an essential feature of the diagnostic method of claim 1 (Guidelines III-4.4).

2 **Claim 24** does not satisfy Art 6 PCT because the scope of the claim is not clear due to the vague expression "...and any additional component required for such assay...".

1 = Lipopolysac
2 = (Alkaline Phosphatase)

19. 01. 2001

AMENDED CLAIMS

(100)

1. A method of diagnosis of onset of endotoxemia or sepsis due to Gram negative bacterial infection said method comprising monitoring of the degree of AP occupancy of LPS binding sites on alkaline phosphatase in a sample of tissue or fluid derived from a patient, wherein the degree of AP occupancy is associated with presence or absence of Gram negative bacterial infection.

2. A method according to claim 1, wherein the degree of AP occupancy of LPS binding sites on alkaline phosphatase in the sample is lower than that of an equivalent sample type of an individual free of Gram negative infection.

3. A method according to claim 1 or 2, wherein the degree of AP occupancy of LPS binding sites on alkaline phosphatase in a sample or tissue or fluid derived from a patient, is monitored over a period of time, wherein a decline of the degree of AP occupancy indicates Gram negative bacterial infection.

4. A method according to any of the preceding claims, wherein the degree of AP occupancy of LPS binding sites on alkaline phosphatase in the sample is determined and wherein onset of decline in the degree of AP occupancy indicates onset of Gram negative bacterial infection.

5. A method according to any of the preceding claims wherein the degree of AP occupancy of LPS binding sites on alkaline phosphatase may also indicate a mixed or single infection of Gram negative and Gram positive bacteria.

6. A method according to any of the preceding claims wherein the sample is subjected to binding with a ligand for the LPS binding site on alkaline phosphatase followed by determination of the degree of binding of the ligand.

7. A method according to any of the preceding claims wherein the ligand for the LPS binding site on alkaline phosphatase is selected from the group consisting of naturally occurring ligands, chemically modified or genetically modified derivatives of natural LPS binding site binding substances, chemically produced ligands.

8. A method according to any of the preceding claims, wherein the sample is subjected to binding with a ligand for the LPS binding site on alkaline phosphatase selected from LPS, Lipid A, an LPS binding site antibody against alkaline phosphatase, a Fab fragment with LPS binding site binding ability on alkaline phosphatase, a single chain fragment of an immunoglobulin having LPS binding site binding activity on

alkaline phosphatase.

9. A method according to any of the preceding claims, wherein the LPS binding site binding ligand has at least the affinity for the LPS binding site of alkaline phosphatase of LPS.

10. A method according to any of the preceding claims wherein the LPS binding site binding ligand has at least the affinity for the LPS binding site of alkaline phosphatase of lipid A.

11. A method according to any of claims 1-5 wherein the degree of AP occupancy of LPS binding sites on alkaline phosphatase is determined by assessment of the dephosphorylating capacity of alkaline phosphatase in the sample.

12. A method according to claim 11, wherein the ratio of dephosphorylating alkaline phosphatase to non dephosphorylating alkaline phosphatase is determined.

13. A method according to claim 12, wherein the ratio is determined using the values obtained by assessment of total alkaline phosphatase activity using biochemical methods to determine dephosphorylating activity and by assessment of total amounts of alkaline phosphatase using e.g. antibodies or otherwise discriminating entities and calculating the ratio of these values.

14. A method according to any of the preceding claims wherein the sample is from a cholestasis free patient.

15. A method according to any of claims 1-13 wherein the method also comprises a further assay of a sample from the patient for another disease related to increase of alkaline phophatase activity, said further assay employing a method avoiding determination of alkaline phosphatase level.

16. A method according to claim 15 wherein the further assay is carried out when no decline in AP occupancy of LPS binding sites of alkaline phosphatase according to the method of any of claims 1-14 is detected.

17. A method according to any of the preceding claims, wherein the sample is taken from an individual at risk of Gram negative bacterial infection.

18. A method according to claim 17 wherein the sample is taken from an individual either both prior to and following trauma or shortly after having undergone trauma, wherein the trauma in particular concerns surgery, burns or ischemic traumas.

19. A method according to any of the preceding claims wherein the sample is taken from an individual during hospitalisation.

20. A method according to any of the preceding claims wherein the sample is taken a number of times over a period of time and the data are compared thus revealing the level of AP occupancy over time.

21. A method according to any of the preceding claims wherein the period of time is as long as the individual is at risk of infection i.e. during hospitalisation or post trauma recovery.

22. A method according to any of the preceding claims wherein the result of the assay is compared to a standard value thus revealing whether the degree of AP occupancy is indicative of endotoxemia or sepsis or the risk thereof.

23. A method according to any of the preceding claims wherein the sample is a sample selected from the group consisting of blood and tissue, said blood sample for example being serum, said tissue being other than bone and said tissue for example being selected from liver and intestine.

~~24. A kit comprising alkaline phosphatase LPS binding site binding ligand~~ and instructions for carrying out an assay according to any of the preceding claims and optionally any additional components required for such assay e.g. detectable marker, buffer, containers and comparative samples or data charts e.g. standard curves or data concerning relevant data of alkaline phosphatase values.

25. A kit comprising alkaline phosphatase LPS binding site binding ligand for carrying out an assay according to any of the claims 1-23 and any additional component required for such assay being selected from the following group consisting of detectable marker, buffer, containers, comparative samples, data charts e.g. standard curves or data concerning relevant data of alkaline phosphatase values.

25. A method for therapy of endotoxemia or sepsis said method comprising administration of a pharmaceutically effective amount of the LPS binding site of alkaline phosphatase in a systemically acceptable form with the proviso the ligand is neither alkaline phosphatase nor a derivative of alkaline phosphatase having dephosphorylating activity.

26. A method for removing LPS from tissue or fluid said method comprising contacting the LPS binding site of alkaline phosphatase with the tissue or fluid to be treated followed by separation of the LPS binding site and the tissue or fluid after the the LPS binding site has bound the LPS present in the fluid or tissue, with the proviso the ligand is neither alkaline phosphatase nor a derivative of alkaline phosphatase having

dephosphorylating activity.

27. A method of purification of AP itself from tissue or body fluids or other biological production systems with a compound with an LPS binding site of alkaline phosphatase such as LPS, lipid A or other ligand as described in the preceding claims.

28. Use of a compound with an LPS binding site of alkaline phosphatase such as LPS, lipid A or other ligand as described in the preceding claims as active compound in a medicament for therapy or diagnosis.

29. Use of a compound with an LPS binding site of alkaline phosphatase such as LPS, lipid A or other ligand as described in the preceding claims as active compound in therapy or diagnosis.

CLAIMS TO REPLACE 24-29 AS FILED

24. A kit comprising alkaline phosphatase LPS binding site binding ligand and instructions for carrying out an assay according to any of the preceding claims and any additional component required for such assay being selected from the following group said group consisting of detectable marker, buffer, containers, comparative samples, data charts e.g. standard curves and data concerning relevant data of alkaline phosphatase values.

25. A method for removing LPS from tissue or fluid said method comprising contacting a compound having a specific binding domain for LPS of alkaline phosphatase with the tissue or fluid to be treated followed by separation of the compound and the tissue or fluid after the compound has bound the LPS present in the fluid or tissue, with the proviso the compound is neither alkaline phosphatase nor a derivative of alkaline phosphatase having dephosphorylating activity.

26. A method for therapy of endotoxemia or sepsis said method comprising administration of a pharmaceutically effective amount of the LPS binding site of alkaline phosphatase in a systemically acceptable form as active compound with the proviso the active compound is neither alkaline phosphatase nor a derivative of alkaline phosphatase having dephosphorylating activity.

27. A method for removing LPS from tissue or fluid said method comprising contacting a compound having a specific binding domain for LPS of alkaline phosphatase with the tissue or fluid to be treated followed by separation of the compound and the tissue or fluid after the compound has bound the LPS present in the fluid or tissue, with the proviso the compound is neither alkaline phosphatase nor a derivative of alkaline phosphatase having dephosphorylating activity.

28. A method of purification of AP from tissue or bodily fluids or other biological system with a ligand which binds to the LPS binding site of AP.

29.A method according to claim 28 wherein the ligand is LPS, lipid A or a ligand which binds to the LPS binding site of AP as described in any of the preceding claims.

30. Use of a compound with an LPS binding site of alkaline phosphatase such as LPS, lipid A or a ligand which binds to the LPS binding site of AP as described in any of the preceding claims as active compound in a method of preparation for a medicament for therapy or diagnosis.

31. Use of a compound with an LPS binding site of alkaline phosphatase such as LPS, lipid A or a ligand which binds to the LPS binding site of AP as described in any of the preceding claims as active compound in a method of preparation for a medicament for therapy or diagnosis of endotoxemia or sepsis.

32. A method for removing LPS from tissue samples or fluid samples said method comprising contacting a compound having a specific binding domain for LPS of alkaline phosphatase with the tissue sample or fluid sample to be treated followed by separation of the compound and the tissue sample or fluid sample after the compound has bound the LPS present in the fluid sample or tissue sample.

33. A method for removing LPS from tissue samples or fluid samples said method comprising contacting a compound having a specific binding domain for LPS of alkaline phosphatase with the tissue sample or fluid sample to be treated followed by separation of the compound and the tissue sample or fluid sample after the compound has bound the LPS present in the fluid sample or tissue sample, with the proviso the compound is neither alkaline phosphatase nor a derivative of alkaline phosphatase having dephosphorylating activity.

34. A method of purification of AP from a tissue sample or a bodily fluid sample or other biological system sample with a ligand which binds to the LPS binding site of AP.

35. A method according to claim 34 wherein the ligand is LPS, lipid A or a ligand which binds to the LPS binding site of AP as described in any of the preceding claims.

36. A method or use according to any of the preceding claims wherein the method is carried out on a sample derived from the group of individuals consisting of a patient, an individual at risk of Gram negative bacterial infection, an individual prior to or after trauma, an individual during hospitalisation.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

JORRITSMA, Ruurd et al.
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PAYS-BAS

19-11-00
19-01-01

WRITTEN OPINION

(PCT Rule 66)

		Date of mailing *(day/month/year)*	19.10.2000
Applicant's or agent's file reference BO 42134		**REPLY DUE**	**within 3 month(s)** from the above date of mailing
International application No. PCT/NL98/00722	International filing date *(day/month/year)* 21/12/1998	Priority date *(day/month/year)* 21/12/1998	
International Patent Classification (IPC) or both national classification and IPC G01N33/569			
Applicant STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN et al.			

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain document cited
   VII ☒ Certain defects in the international application
   VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also: For an additional opportunity to submit amendments, see Rule 66.4.
   For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
   For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 21/04/2001.

Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer / Examiner Tilkorn, A-C Formalities officer (incl. extension of time limits) Danti, B Telephone No. +49 89 2399 8161

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-12 as originally filed

Claims, No.:

1-29 as originally filed

Drawings, sheets:

1/1 as originally filed

T97/00935
T97/1173.

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 25', 27-29 with respect to N, IS and claim 25', 26-29 with respect to IA,

because:

☒ the said international application, or the said claims Nos. 25',26-29 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 25',27-29 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	24,25,26
Inventive step (IS)	Claims	
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

1 **Claims 25'** and **27** are so unclear that no meaningful opinion can be formed on novelty and inventive step (Art 34 (4)(a)(ii) PCT; Guidelines VI-5.11)
Claim 25' is directed to a method that involves the administration of an LPS binding site. It is unclear, as to what the disclaimer refers, since no mention is made to a ligand in the first part of the claim.
Claim 27 relates to the purification of AP wherein a compound is used that has the LPS binding site of alkaline phosphatase. Examples given are ligands of AP. The compound can either have an LPS binding site of AP or be a ligand of AP. In other words compounds with an LPS binding site of AP are the counterparts of LPS, lipid A and other AP ligands. Thus, **claim 27** is contradictory in itself and its subject-matter is thus not defined. The same argument applies to **claims 28** and **29**.

2 The subject-matter of **claim 25'** is considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (Guidelines IV-2.4(d)).
For the assessment of said claim on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
The same argument applies to **claims 26** and **27** which relate to methods which might be carried out in vivo. In order to exclude in vivo methods the claims could be reformulated such that they relate to methods involving tissue samples or fluid samples.
Claims 28 and **29** are also directed to therapeutic methods and thus fall under the provisions of Rule 67.1(iv) PCT).

Re Item V

The following documents are referred to in this communication:

D1: WO 95 05456 A (cited in the application: p 2 l 24; p 3 l 3)

A copy of D1 is appended to this communication.

1 Novelty (Art 33(2) PCT):

1.1 **Claim 24** is not novel for the following reasons:
A kit alone is not considered to contain a technical feature. Alkaline phosphatase ligands are known in the art, e.g. lipid A (see e.g. D1: p 1 l 25-27; p 11 l 26-33) . Instructions for carrying out an assay are not considered to be a technical feature. Optional features do not restrict the scope of the claim. Thus, the only technical feature is an alkaline phosphatase ligand, which is not new.
The same arguments apply to **claim 25**, which is not considered novel, either.

1.2 **Claim 26** is not novel in view of D1, in which a method comprising the same essential features is claimed (D1: claim 40). A substance as referred to in D1 can be a tissue or fluid sample.

1.3 **Claim 1** is novel, because none of the available documents discloses a method of diagnosis of sepsis or endotoxemia by monitoring the degree of occupancy of LPS binding sites on alkaline phosphatase in a sample. Accordingly, **claims 2-23** are novel.

2 Inventive Step (Art 33(3) PCT):

2.1 The subject-matter of **claim 1** seems to satisfy Art 33(3) PCT:
The present invention is based on the observation of product inhibition of alkaline phosphatase (p 10 experiment IV). The concept of the invention thus consists of determining the ratio of active alkaline phosphatase to non-active ligand bound AP (p 5 l 13-22) in order to diagnose gram negative bacterial infection.
D1, which is considered to represent the closest prior art, describes the correlation between alkaline phosphatase activity and gram negative bacterial infection namely the increase in AP activity due to gram negative bacterial infection.(D1: Fig. 6 p 21 l 32- p 22 l 7). AP activity is measured with standard methods.
The problem to be solved by the method of claim 1 can thus be regarded as the

provision of an alternative method for the diagnosis of endotoxemia or sepsis due to gram negative bacterial infection.
Since the product inhibition of AP has not been known at the priority date, the claimed method is not rendered obvious by any piece of prior art.
Accordingly, **claims 2-23** seem to be inventive, too.

Re Item VII

The expression "incorporated herein by reference" in respect of prior art documents (e.g. page 5 l 23, page 6 l 12) leads to a doubt as to whether the requirement of the description being self-contained is satisfied (Guidelines II, 4.17).

Re Item VIII

1 The numbering of the claims is not correct since there are two **claims 25**. In this communication, the claim which relates to a method for therapy is referred to as claim 25'.

2 **Claim 1** does not satisfy Art 6 PCT because the abbreviation "AP" is not clear. To overcome this objection, in the first instance of its use, the abbreviation should follow in brackets after the complete expression "alkaline phosphatase". Similarly, at least one independent claim should contain the expression "lipopolysaccharide (LPS)".

3 The additional technical feature contained in **claim 2** consists of the assessment of the result obtained by determining the degree of AP occupancy of LPS binding sites on alkaline phosphatase (claim 1) and thus appears to be an essential feature of the diagnostic method of claim 1. Therefore, the subject-matter of claim 2 should be introduced into claim 1 (Guidelines III-4.4).

4 **Claim 26** is not supported by the description (Art 6 PCT), since the application does not contain any data which would demonstrate that AP can bind to the LPS binding site on AP.